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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/842,111	04/26/2001	Kathleen D. Danenberg	11220/128	6762

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EXAMINER	
FREDMAN, JEFFREY NORMAN	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/842,111	DANENBERG, KATHLEEN D.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,10,11,17,20,22,27-29,31-35 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6, 10, 11, 17, 20, 22, 27-29, 31-35, 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7, 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status

1. Claims 6,10,11,17,20,22,27-29,31-35 and 37 are pending.

Claims 6,10,11,17,20,22,27-29,31-35 and 37 are rejected.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Priority

2. This amendment satisfies the priority claim and priority is now fully granted.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 6,10,11,17,20,22,27-29,31-35 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al (U.S. Patent 6,015,673) in view of Willhauck et al (Biotechniques (1998) 25:656-659) and further in view of Stanta et al (Biotechniques (1991) 11(3):303, 306, 308).

Gonzalez teaches a method for determining the level of DPD gene expression in a tissue to determine the safety of a 5-fluorouracil based chemotherapeutic regimen comprising the steps: (see column 14, lines 41-51, also see column 27, lines 14-27, here the tissue is cultured fibroblasts derived from skin biopsies),

(a) obtaining a sample from a patient (column 14, lines 41-52)

(b) isolating mRNA from the sample (column 14, lines 52-67),

(c) amplifying the mRNA with primers which are substantially identical to SEQ ID NO: 1 and 2 (see column 55, SEQ ID NO: 5)

a sequence, SEQ ID NO: 5, which is a sequence substantially identical to the claimed SEQ ID NO: 1 as shown in the alignment below.

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Gonzalez SEQ ID NO: 5 -    GCAAGGAGGGTTTGTCACTG
                           ||||||||||||||||
Claimed SEQ ID NO: 1 AGGACGCAAGGAGGGTTTG
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As the alignment shows, the Gonzalez sequence is 14/19 nucleotides identical to the claimed sequence, for a homology over the claimed sequence of 73%. Further, all of the SEQ ID NO:s are substantially identical to the human DPD sequence disclosed in SEQ ID NO: 1 of U.S. Patent 5,856,454 and are derived from that sequence. Gonzalez teaches the full sequence from which the primers were derived.

Gonzalez teaches freezing of the sample (see column 25, line 64) as well as fixing of the sample for detection (see column 13, lines 46-53).

Gonzalez teaches isolation of mRNA in the presence of Guanidine, a chaotropic agent (column 14, lines 52-67).

Gonzalez teaches that appropriate samples include any cells from the patient that may express the DPD gene (column 14, lines 41-51).

Gonzalez teaches a threshold for the mutation in which there is a problem tolerating 5-fluorouracil based chemotherapeutic regimens where a 2 fold difference will yield enhanced risk (see column 15, lines 1-11)

Gonzalez does not teach step (d) comparing the amount of DPD mRNA to the amount of mRNA of an internal control gene.

Willhauck teaches comparing the amount of the target gene to an internal control gene including B-actin (see page 656, columns 1-3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the internal controls of Wilhauck in the method of Gonzalez since Wilhauck states "Taken together our results show that the internal control circumvents a number of inherent problems of alternative controls to assess pre-PCR procedures. The overall RT-PCR assay sensitivity can be reliably evaluated on a per sample basis and the sensitivity limit of the RT-PCR assay can be assessed for every sample. This type of reliability can improve the homogeneity of results from clinical investigations in the future (page 658, column 3 to page 659, column 1)". An ordinary practitioner would have been motivated to use the internal controls of Wilhauck in the method of Gonzalez in order to reliably and sensitively improve the homogeneity of the clinical results.

While Gonzalez discussed analysis of fixed samples (see column 16, line 63 to column 17, line 5), neither Gonzalez nor Wilhauck teach the standard methods for analysis of RNA from fixed and paraffin embedded samples by PCR.

Stanta teaches a method of extracting RNA from paraffin embedded human tissues comprising:

a) fixing and paraffin embedding tissue samples (see page 304, column 2),

b) isolating mRNA from the FPE tissue sample (see page 304, column 2),

c) amplifying the mRNA by RT-PCR (see page 304, columns 2 and 3).

With regard to the use of a chaotropic agent, Stanta teaches the use of guanidinium thiocyanate in the isolation buffer (see page 304, column 2).

With regard to the specific temperature ranges given for the isolation and to the specific time ranges claimed, Stanta teaches a variety of times and temperatures. In the remaining claims, given the absence of any evidence that the time frame or the specific temperature range has any unexpected properties, an ordinary practitioner would have recognized that the results optimizable variables of time and temperature, could be adjusted to maximize the desired results, whether maximal release of RNA by use of higher temperatures or longer times or maximum speed by use of higher temperatures and shorter times, or maximum care by use of lower temperatures and longer times. These variables are known to directly effect the release of the RNA from the paraffin embedded samples. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific times for amplification was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the method of Stanta in the method of Gonzalez in view of Wilhauck since Stanta teaches "The accessibility of paraffin embedded material for RNA analysis opens the archives of the hospital pathology departments to RNA expression or RNA virus persistence analysis and allows the study of a large number of cases of more or less rare diseases. The method could also be useful for diagnostic procedures with the advantage that it is not necessary to change the usual methods to store human tissues in the hospitals (see page 308, column 2)." Thus, Stanta expressly suggests an advantage in diagnostic applications such as those of Gonzalez, specifically motivating the use of Stanta's method with Gonzalez's diagnostic application by permitting the method to operate with a change of the usual storage method in hospitals.

Response to Arguments

5. Applicant's arguments filed May 26, 2004 have been fully considered but they are not persuasive.

Applicant questions whether the rejection addresses the claims since it uses the term "substantially identical" while the claims have had this phrase deleted. This is not relevant since the references cited render the claims obvious whether they use the phrase "substantially identical" or not. It is clear that the rejection was amended by the inclusion of the Stanta reference, to address the actual significant new limitations drawn to the use of FPE tumor samples.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the current case, Applicant's analysis fails to analyze the combination of references as a whole. Gonzalez teaches a method of analysis of DPD expression by amplifying mRNA with primers selected from the DPD gene in order to determine the safety of a 5-fluorouracil chemotherapeutic regimen. Gonzalez expressly teaches and suggests the application of the method to fixed samples (see column 16, line 63 to column 17, line 5). So Gonzalez only does not teach the specific method of detection from FPE cells. This element is expressly taught and suggested by Stanta, as discussed in the rejection above.

When Applicant argues that Wilhauck teaches away from the invention, Applicant is mischaracterizing the Wilhauck reference. Wilhauck repeatedly states that internal controls are desirable and that B-actin is a functional internal control. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Wilhauck had a preferred embodiment

regarding which internal control to use, this embodiment does not prevent the use of alternative embodiments or constitute a teaching away from such embodiments such as those suggested by the B-actin, also expressly taught by Wilhauck.

Applicant then argues that Stanta teaches away from the invention. This is clearly not the case for any of the generic claims, such as claim 6, in which none of the conditions of the extraction are required. However, as noted in the rejection, even for the specific times, such elements are routinely optimizable. Applicant has provided no evidence that selection of 50 C as a temperature, for example, does not simply represent routine optimization of Stanta's teaching of 45 C. The rejection cites *In re Aller*, 105 USPQ 233 at 235 for the proposition that,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and the specific times and temperatures appear to simply represent such routine experimentation. There is no evidence of any secondary consideration regading such times and temperatures.

For these reasons, the rejections are maintained.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
6/3/06